Nitrogen Metabolism

Introduction

Nitrogen is what makes protein. It is the **amino** of **amino acids**. All cells have protein. Every enzyme is a protein. Every cell has transports, channels, receptors, hormones, etc. Every cell must metabolize protein, and every cell must handle nitrogen. Nitrogen, on its own (NH_3) is unfriendly to cells in general. The **only cells that can handle free NH_3** are the **liver** and the **kidney**. Unsurprising, then, that the **liver metabolizes 90% of the body's nitrogen** while the **kidney both metabolizes (10%) and eliminates nearly 100% of it**. The nitrogen game seems almost too simple. There are so few players used in the same way in different tissues it almost isn't fair. But because this is usually saved for the end of metabolism, and because we go back and forth between amino acids (which have an amino group) and keto acids (the same acid without its amino group), it gets really confusing. And it's also a lie. We are going to follow nitrogen from amino acid to elimination. Elimination happens via **NH_4^+** in the urine and as **urea** in the urine, made by the liver. The "lie" is that the **urea cycle** is listed as "the urea cycle" in this lesson. In the next lesson (Metabolism #19: *Urea Cycle*) we'll explore in detail the steps in the process of how urea gets made, and the deficiencies found therein. Then in the final nitrogen lesson (Metabolism #20: *Amino Acid Catabolism*) we will explore the "truth" of amino acid metabolism, introducing quite complex pathways and genetic disorders.

Ins and Outs of Nitrogen

Input of nitrogen to the human body is from **dietary protein**. It's the only way nitrogen gets in. Nitrogen goes to many places and there is recycling of that nitrogen, but nitrogen comes in through diet. That means all nitrogen comes **through the liver first** and then enters portal circulation.

Output of nitrogen from the human body is in the form of **urea in the urine** (urea produced by the urea cycle in the liver) and as **ammonium** (NH_4^+ produced by glutamine shuttling of amino groups to the kidney). When the liver is dysfunctional, medications can trap excess nitrogen in the gut for elimination. Really, we limit the intake of nitrogen reducing the in, but there is a small component of output involved in there. The elimination of nitrogen from the urea cycle represents 90% of nitrogen metabolism. Less than 10% is managed by the glutamine-NH_3-urine system.

If there is a nitrogen imbalance, and **ammonia accumulates** in the body, it is toxic. It gets trapped in cells (such as the brain, behind the blood-brain barrier) by becoming NH_4^+. NH_4^+ is both toxic itself and is osmotically active. Ammonia accumulates when there is either **liver failure** (cirrhosis or acute) or **renal failure** (ESRD or acute kidney injury). Not surprisingly, both will present with the same neural stuff—**hepatic encephalopathy** and **asterixis**.

Labs can help determine whether liver or kidney is the cause. If there is acute liver damage then the aminotransferase of the liver (below), **alanine amino transferase (ALT)** and **aspartate aminotransferase (AST)** will be elevated on liver function tests (LFTs or CMP). Signs that the rise in nitrogen is because of the kidneys is the **blood urea nitrogen (BUN)** found on a BMP.

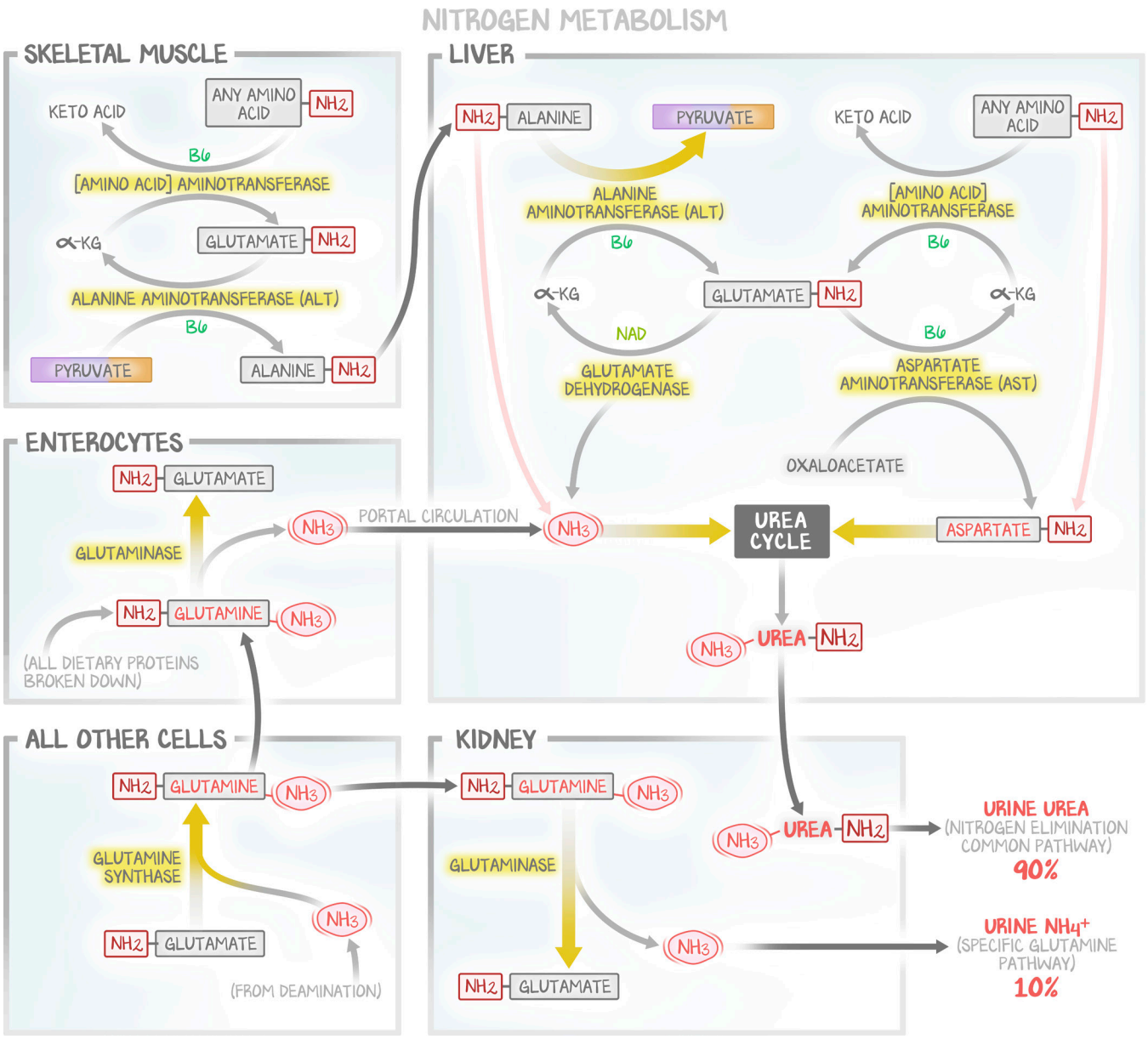

Figure 18.1: Nitrogen Metabolism
This is how the various cells handle excess nitrogen. Most tissues rely on glutamine synthetase and give the amino acid to someone else. The liver is the most potent organ in managing nitrogen, and is the site of the urea cycle. The kidneys do all the urea elimination and some nitrogen elimination. Skeletal muscle is the source of protein the liver can use.

Major Players in This Game

Glutamate is seen in **every cell**. It's always a metabolite, an intermediate step. Glutamate has one amino group. Remove that amino group and it becomes α-ketoglutarate (α-KG). Add an amino group to glutamate and **it becomes glutamine**.

Glutamine is how **dumb cells send nitrogen around**. Most cells in the body are "dumb." The ones that aren't dumb are enterocytes and kidney cells. They process glutamine. Free NH_3 is bad for every cell except the liver. So instead of trying to move around NH_3, cells instead take a glutamate and add that

excess NH_3 to it, and make glutamine. I like to imagine "all other tissues" like a sitcom character with arachnophobia. The spider is nitrogen. Whenever these cells see nitrogen, they freak out, jump on the table, and do everything can to get the spider out of the house. That panic-get-rid-of-it is glutamine. To do this, "all other tissues" have one trick—**glutamine synthetase**; they add that amino to a glutamate and throw it into circulation.

Glutamine is how **smart cells receive nitrogen**. They are the ones that calm down that sitcom character, taking the upturned house and righting it again. Calmly, slowly, the enterocytes and kidney cells simply undo the damage. **Glutaminase** (glutamine-ase) liberates that free NH_3, recycling glutamate. Then they process that NH_3.

The **intestinal cells** send **free NH_3 into portal circulation**. The liver gets it, knows how to process it, and takes care of it with the urea cycle. The **renal cells** take that NH_3 and send it into the urine. NH_3 is nonpolar, and it can cross membranes. The kidneys **trap NH_3** in the urine as **NH_4^+**, which is no longer lipophilic, so becomes trapped in the urine.

In every cell that had glutamine there was a pairing with glutamate. Either glutamine is built from glutamate by adding an NH_3, or glutamate is made by removing an NH_3 from glutamine. Be careful, though—glutamate is used in far more processes than that. The presence of glutamine, glutaminase, or glutamine synthase means there is a glutamate around; but the presence of glutamate does NOT mean glutamine is around.

Major Players in Skeletal Muscle and Liver

The two cells we saved for the end are the **skeletal muscle** (they are nitrogen/aminos and glycogen) and the **liver** (the epicenter of metabolism). These cells aren't just glutamine-smart, they are doctoral candidates in protein in general. Skeletal muscle can send protein to the liver for catabolism, and the liver can do much with those proteins (see Metabolism #20: *Amino Acid Catabolism*). For now, our focus is on management of excess nitrogen.

Skeletal muscles know how to shuttle protein between muscle and liver (alanine) and also how to shuttle nitrogen around **its own cell**, between the amino acid and the keto acid. In this process, the nitrogen is just moved around until it gets to a form that can be sent to the liver. For this discussion, **alanine** is the only and final product that is sent to the liver. An enzyme that **moves amino around** is called an **aminotransferase**. These enzymes are called [amino-acid-giving-NH_3] aminotransferase except when it includes glutamate—then it's whatever the other amino acid is. This is because these are **reversible reactions** and science has chosen to name them this way. Aminotransferases catalyze reversible reactions, and all require **vitamin B_6** to function. All of them.

The first step is [**generic**] **aminotransferase**, which takes that amino group and adds it to **α-KG** (a keto acid), making **glutamate**. The aminotransferase is named by the amino acid that gives the NH_3 to glutamate. Glutamate is a substrate or metabolite in every cell within nitrogen metabolism. The glutamate acts as an **intermediary** holding onto the NH_3 until it can be transferred onto **pyruvate**, **making alanine**, catalyzed by **alanine aminotransferase**. "Alanine aminotransferase" because the transfer of nitrogen involves glutamate, so the transferase is named for the other amino acid, in this case alanine.

Liver cells are of course the most complicated. They take **dietary NH_3** and immediately put it into the **urea cycle**. The incoming **alanine** is used in exact reverse of the skeletal muscle. Alanine is converted **back to pyruvate** (which can be used to make glucose), donating its amino group to α-ketoglutarate to make **glutamate**. This process is also **alanine aminotransferase**. From here, there are two possible steps that glutamate can take. Both paths lead back to α-KG. **Glutamate dehydrogenase** takes an

NAD and makes **NADH** and free **NH_3**. That free NH_3 goes into the urea cycle just like the dietary NH_3. ("Glutamate dehydrogenase," named glutamate because it involves glutamate but isn't an aminotransferase.) **Aspartate aminotransferase** donates the glutamate NH_2 group from oxaloacetate to make **aspartate**. ("Aspartate aminotransferase" because it involves glutamate, so named for the other amino acid.) **Aspartate** can then **enter the urea cycle** at a different point than NH_3.

The result of the urea cycle is **urea**. It goes to the kidneys for elimination.

Conclusion

Aminotransferases, alanine (muscle, liver) and aspartate (liver) are what skeletal muscle and liver use to metabolize nitrogen. The liver can metabolize NH_3 and aspartate to urea. The kidneys eliminate urea and NH_4^+. The intestines and kidneys break down the "panic compound" glutamine back to glutamate and NH_3 using glutaminase. The intestines send that NH_3 to the liver for processing. The kidneys eliminate it. Every other cell uses glutamine synthetase to make glutamine from glutamate, the "panic compound."